Associations between radiographic characteristics and change in renal function following partial nephrectomy using 24-hour creatinine clearance

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Abstract

Background: Radiographic characteristics may be associated with the degree of renal function preservation following partial nephrectomy. The purpose of this study was to determine the impact of preoperative radiographic variables on change in renal function using 24-hour urine creatinine clearance (uCrCl).

Methods: Patients with partial nephrectomy performed from November 2003 to 2008 were enrolled in the study. Serum creatinine and 24-hour urine was collected preoperatively and at 3, 6 and 12 months postoperatively. Computed tomography or magnetic resonance imaging was used to determine tumour size, tumour location and renal volume.

Results: Of the 36 patients, median age was 62 (range 30-78) and 21 (58%) were male. The mean tumour diameter was 2.8±1.4 cm. Twenty-two (61%) tumours were located at the renal pole and 11 (31%) were endophytic. Overall, mean preoperative uCrCl was 88.8±34.2 mL/min and mean postoperative uCrCl was 82.8±33.6 mL/min (6.8%; $p < 0.01$). On multivariable analysis, no single characteristic was associated with a clinically prohibitive decrease in renal function (-9.4% if endophitic, $p = 0.06$; -0.57% per cm diameter, $p = 0.73$; and -6.9% if located at the renal pole, $p = 0.15$). The total renal volume was also not significantly associated with renal function change (-1.1% per 100 cc, $p = 0.86$).

Interpretation: Preoperative radiographic characteristics seem to be associated with small changes in renal function following partial nephrectomy. These data support renal functional benefits of partial nephrectomy regardless of tumour size and location.

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Résumé

Contexte : Les caractéristiques radiographiques peuvent être associées au niveau de préservation de la fonction rénale après une néphrectomie partielle. L'objectif de l'étude était d'évaluer l'impact de variables radiographiques préopératoires sur les variations de la fonction rénale à l'aide de la mesure de la clairance de la créatinine dans les urines recueillies sur 24 heures (ClCrU).

Méthodologie : Des patients ayant subi une néphrectomie partielle entre novembre 2003 et 2008 ont été admis à l'étude. On a mesuré la créatinine sérique et recueilli les urines sur 24 heures avant l'opération, puis 3, 6 et 12 mois après l'opération. La taille et le siège de la tumeur et le volume rénal ont été déterminés par tomographie par ordinateur ou par imagerie par résonance magnétique.

Résultats : L'âge médian des 36 patients admis était de 62 ans (entre 30 et 78 ans); 21 patients (58 %) étaient des hommes. Le diamètre moyen de la tumeur était de 2,8 ± 1,4 cm. Vingt-deux tumeurs (61 %) étaient situées à un pôle rénal et 11 (31 %) étaient endophytiques. De façon globale, la ClCrU moyenne avant et après l'opération était de 88,8 ± 34,2 mL/min et de 82,8 ± 33,6 mL/min (6,8 %; $p < 0,01$), respectivement. Selon l'analyse multivariée, aucune caractéristique particulière n'était associée à une réduction cliniquement excessive de la fonction rénale (-9,4 % pour les tumeurs endophytiques, $p = 0,06$; -0,57 % par cm de diamètre, $p = 0,73$, et -6,9 % si la tumeur était située à un pôle rénal, $p = 0.15$). Le volume rénal total n'était pas non plus associé de façon significative à une variation de la fonction rénale (-1,1 % pour 100 mL, $p = 0.86$).

Interprétation : Les caractéristiques radiographiques préopératoires semblent associées à de petites variations de la fonction rénale après une néphrectomie partielle. Ces données appuient les avantages liés à la fonction rénale de la néphrectomie partielle, peu importe la taille et le siège de la tumeur.

Introduction

Surgical excision is the most effective treatment for patients with primary renal malignancy. In the past, partial nephrectomy was performed exclusively on patients with a solitary kidney, bilateral renal tumours or renal insufficiency. However, this operation is now preferred in many other patients given equivalent cure rates compared to radical nephrectomy.[1-7] Moreover, recent data reveal that partial nephrectomy patients with a normal contralateral kidney and normal preoperative renal function have improved long-term renal function[2,8-11] and possibly improved overall survival.[12,13] Thus, the most recent American Urological Association guideline recommends partial nephrectomy as the treatment of choice for the management of clinical stage 1 renal masses, even in those with a normal contralateral kidney.[14]

Despite the advantages over radical nephrectomy, partial nephrectomy also results in loss of functioning nephrons due to resection of normal parenchyma, intraoperative ischemia

and other physical/chemical trauma secondary to surgery. Since, tumour size and location may predict the severity of nephron loss, these measurements may be important variables in determining which patients will benefit most from partial nephrectomy.[10] Furthermore, the proportional loss in renal function may depend on the baseline contribution of renal function from the affected kidney. Despite the theoretical utility of kidney and tumour characteristics, the association between preoperative radiographic findings and loss of renal function has not been adequately investigated.

Direct measurements of glomerular filtration rate (GFR) are uncommonly performed on partial nephrectomy patients. Therefore, most partial nephrectomy renal function studies rely on estimates of glomerular filtration based on serum creatinine, such as the Modification of Diet in Renal Disease (MDRD) or Cockroft-Gault equations. While estimates of glomerular filtration may be adequate in most situations, these methods may be insensitive to longitudinal changes in renal function.[15,16] To detect small but clinically important differences in renal function, other methods of assessing glomerular filtration, such as urine creatinine clearance, may be necessary. The purpose of this study was to determine the association between preoperative renal and tumour characteristics and change in creatinine clearance following partial nephrectomy.

Methods

This study was approved by the institutional review board. Consecutive patients referred to a single urologic oncologist (IC) at the University of Ottawa (Ottawa, Ontario, Canada) with an enhancing renal mass between 2003 and 2008 were enrolled in this renal function study. Patients with an organ-confined, sporadic, solitary tumour (<4 cm or <7 cm if the patient had a GFR <60 mL/min) and normal appearing contralateral kidney were offered an open partial nephrectomy. Patients receiving renal replacement therapy were excluded. Patients were also excluded if they had previous renal surgery, had a solitary kidney or multiple renal tumours at presentation (excluding renal cysts).

In all cases, the kidney was approached using a supra-11th rib mini-flank incision. The rib was not resected. Mannitol (12.5 g) was administered about 5 minutes prior to renal ischemia. The hilar arteries and veins were occluded using bulldog clamps and 10 minutes of renal hypothermia was achieved using saline slush prior to tumour resection and renorrhaphy.

The GFRs, based on creatinine clearance measurements, were assessed preoperatively and 3, 6 and 12 months postoperatively (GFR = [24-hour urine creatinine concentration × 24-hour urine volume] / [serum creatinine × 1440 min/day]). The primary outcome was relative difference in GFR ([postoperative GFR – preoperative GFR] / preoperative GRF). We previously observed that GFR remains stable between 3 months and 12 months post-partial nephrectomy;[17] therefore, postoperative GFR was considered the average of the 3 postoperative renal function assessments.

We identified, a priori, the following potential radiographic predictors of change in GFR: maximal tumour diameter, tumour location (pole or mid-pole), tumour depth (60% within the parenchyma considered endophytic[18]) and renal volume ($L \times W \times H / 6) \times \varpi$). All tumour and kidney metrics were obtained from preoperative abdominal computed tomography or magnetic resonance imaging without knowledge of renal function outcomes.

Univariate and multivariable linear regression analyses were performed for all predictor variables. Common variance and approximate normality assumptions were visually assessed using model residuals. All comparisons are presented with 95% confidence intervals to assess for clinically meaningful type II error. Risk of type I error was set at 5% with a p value of less than 0.05 considered statistically significant.

Results

Forty-nine patients received a partial nephrectomy during the study period and 36 qualified for the study. Five patients were excluded because they had a solitary kidney, 3 had bilateral tumours, 3 were non-compliant with urine collections and 2 were lost to follow-up. Preoperative patient and tumour characteristics are presented in Table 1. The contralateral kidney volume was similar to the volume of the kidney with the tumour in most patients (contralateral kidney volume: affected kidney volume; median 1.0; interquartile range [IQR] 0.86-1.15). The median cold ischemic time (including 10 minutes of cooling) was 37 minutes (IQR: 32-43) and average estimated blood loss was 284 ± 157 mL. All cases had negative tumour margins and, histologically 12 (46%) were clear cell renal cell carcinoma, 9 (35%) were papillary renal cell carcinoma, 2 (8%) were chromophobe renal cell carcinoma, 2 (8%) were oncocytoma and 1 (4%) was angiomyolipoma. No patient required completion nephrectomy and no patient required renal replacement therapy during the study period. At 1-year follow-up, no patient experienced local or distant tumour recurrence.

Overall, the mean decrease in GFR was 5.7 mL/min which corresponded to a 6.8% relative decrease in renal function following partial nephrectomy ($p < 0.01$). On univariate and multivariable analysis, larger kidney volume, greater tumour diameter, endophytic tumours and tumours located in the renal pole were associated with worse renal function outcome (Table 2). However, the associations were not statistically significant and only tumour depth seemed to represent potential clinical significance.

Table 1. Baseline characteristics of partial nephrectomy patients

	Partial nephrectomy (n=36)
Age in years: median (IQR)	62 (52 - 69)
Male	21 (58%)
Preoperative GFR: mean (SD)	89 (35) mL/min
Left side	19 (53%)
Affected kidney volume: mean (SD)	174 (35) cm^3
Contralateral kidney volume: mean (SD)	171 (47) cm^3
Tumour diameter: mean (SD)	2.8 (1.4) cm
Endophytic	11 (31%)
Located in kidney pole	22 (61%)

IQR: interquartile range; GFR: glomerular filtration rate; standard deviation.

Discussion

As the technical and indication boundaries of partial nephrectomy expand, cancer control and short-term complication rates have been closely scrutinized.[3-5,7] However, it is unclear which patients will have the best or worst renal function outcomes postoperatively. Many urologists may not perform laparoscopic partial nephrectomy on large or endophytic tumours. Therefore, some must choose between a laparoscopic radical nephrectomy and an open partial nephrectomy. Since a flank incision may be associated with a more complicated and lengthy convalescence, the inherent risks of open partial nephrectomy need to be carefully balanced with potential benefits.

Traditionally, in the setting of a normal contralateral kidney, radical nephrectomy was considered the best treatment for patients with primary renal malignancy. It was believed that maintenance of renal function was not a concern in these patients since transplant donors do not seem to have an increased incidence of renal failure compared to the overall population.[19,20] However, transplant patients are highly selected healthy individuals and patients with renal tumours often have significant comorbid disease, which is highlighted in recent studies that reveal higher rates of long-term renal insufficiency and mortality in radical nephrectomy patients compared to partial nephrectomy patients.[9,12,13]

In the present study, we attempted to identify preoperative radiographic factors associated with renal function change. Importantly, we did not identify characteristics that prohibited the use of partial nephrectomy; our findings reaffirm the effectiveness of partial nephrectomy at preserving renal function, as average postoperative GFR was only 6.8% less than preoperative measurements. For example, after adjusting for covariates, a 1-centimeter difference in tumour size was associated with a 0.6% decrease in renal function. Therefore, on average, a partial nephrectomy for a 5-centimeter tumour results in less than a 2% predicted decrease in renal function compared to a partial nephrectomy for a 2-centimeter tumour. Furthermore, if we consider the lower 95% confidence limit for renal size (3.9% decrease in GFR per cm), the predicted decrease in renal function for the above scenario would result in an 11.7% decrease in renal function. Given that radical nephrectomy usually results in a 30% to 40% loss of estimated GFR,[2,8-11] it seems that patients functionally benefit from partial nephrectomy regardless of tumour size.

The associations between change in renal function and tumour size and location have been reported in other studies.[18,21-23] In these reports, the effect of tumour diameter were considered after adjusting for operative variables, including ischemic time. Nevertheless, most of the model coefficients from these studies were consistent with our findings. For example, other authors have not observed statistical or clinical differences in renal function associated with tumour size (0.7 to 1.9 mL/min for every centimeter increase in tumour size).[18,21-23]

The association between endophytic tumours and worse postoperative renal function may be secondary to unadjusted confounders, such as volume of functioning parenchyma resected. Song and colleagues evaluated the effect of renal volume reduction and observed the proportion of renal volume resected was the strongest predictor of change in renal function following partial nephrectomy (0.95% decrease in GFR for every percent decrease in renal volume; 95% CI 0.74 to 1.16).[18] When the authors adjusted for potential confounders, including warm ischemic time and percent decrease in renal volume, the association between endophytic tumours and renal function change became clinically insignificant (1.49% decrease in GFR; 95% CI 1.26% to 4.24%). To avoid incision of an endophytic tumour, it has been our practice to incise the renal capsule at the estimated deep perimeter of the tumour (based on preoperative imaging or intra-operative ultrasound), thus, more normal parenchyma was likely excised in these cases compared to mesophytic or exophytic tumours.

Clearance of endogenous (i.e., creatinine) or exogenous (i.e., ^{99m}Tc-

Table 2. Effect of preoperative characteristics on change in renal function based on univariate and multivariable analysis

	Univariate		Multivariable	
	Coeffecient (95% CI)	*p* value	Coeffecient coeffecient (95% CI)	*p* value
Tumour diameter	-0.75% per cm (-4.1 to 2.6)	0.66	-0.57% per cm (-3.9 to 2.8)	0.73
Depth	-8.7% if endophytic (-18.2 to 0.8)	0.07	-9.4% if endophytic (-19.0 to 0.3)	0.06
Location	-6.2% if at pole (-15.5 to 2.9)	0.18	-6.9% if at pole (-16.2 to 2.5)	0.15
Renal volume	-1.5% per 100 cm^3 (-15.2 to 12.3)	0.82	-1.1% per 100 cm^3 (-14.6 to 12.3)	0.86

CI: confidence interval.

DTPA) substances are regarded as the most valid methods to assess renal function.[24] While preferred to serum creatinine equations (i.e., Cockroft-Gault), urine clearance may also be inaccurate if patients do not properly collect urine specimens. To reduce risk and influence of error, we reinforced proper collection methods during patient consultations and averaged the results of 3 postoperative investigations to determine renal function. Nonetheless, more expensive and invasive tests, such as clearance of radioisotopes (^{99m}Tc-DTPA, ^{51}Cr-EDTA and ^{125}I-iothalamate), have reduced risk of measurement error and may be considered in future partial nephrectomy studies.

While our observations are consistent with previous studies, several methodologic limitations should be considered. All of these cases were performed using renal hypothermia and associations may differ if warm ischemia is used. In addition, generalizations should only be applied to patients with comparable preoperative characteristics. Lastly, the association between preoperative characteristics and postoperative renal function likely fall within the confidence intervals presented. When the confidence interval includes clinically meaningful associations, such as the case for tumour depth, further definitive studies are required.[25]

Conclusion

Partial nephrectomy in the setting of a functioning contralateral kidney results in a small decrease in overall renal function. Compared to historical radical nephrectomy outcomes, the preservation of renal function was favourable regardless of tumour size and location. Partial nephrectomy should be considered in all patients with organ confined, surgically amenable tumours and a normal contralateral kidney.

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References

1. Herr HW. Partial nephrectomy for unilateral renal carcinoma and a normal contralateral kidney: 10-year followup. *J Urol* 1999;161:33-4; discussion 4-5.
2. Dash A, Vickers AJ, Schachter LR, et al. Comparison of outcomes in elective partial vs radical nephrectomy for clear cell renal cell carcinoma of 4-7 cm. *BJU Int* 2006;97:939-45.
3. Mitchell RE, Gilbert SM, Murphy AM, et al. Partial nephrectomy and radical nephrectomy offer similar cancer outcomes in renal cortical tumours 4 cm or larger. *Urology* 2006;67:260-4.
4. Leibovich BC, Blute ML, Cheville JC, et al. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. *J Urol* 2004;171:1066-70.
5. Becker F, Siemer S, Hack M, et al. Excellent long-term cancer control with elective nephron-sparing surgery for selected renal cell carcinomas measuring more than 4 cm. *Eur Urol* 2006;49:1058-63; discussion 63-4.
6. Thompson RH, Siddiqui S, Lohse CM, et al. Partial versus radical nephrectomy for 4 to 7 cm renal cortical tumours. *J Urol* 2009;182:2601-6.
7. Breau RH, Crispen PL, Jimenez RE, et al. Outcome of stage T2 or greater renal cell cancer treated with partial nephrectomy. *J Urol* 2010;183:903-8. Epub 2010 Jan 18.
8. Lau WK, Blute ML, Weaver AL, et al. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. *Mayo Clin Proc* 2000;75:1236-42.
9. Huang WC, Levey AS, Serio AM, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol* 2006;7:735-40.
10. Tanaka N, Fujimoto K, Tani M, et al. Prediction of postoperative renal function by preoperative serum creatinine level and three-dimensional diagnostic image reconstruction in patients with renal cell carcinoma. *Urology* 2004;64:904-8.
11. Zorn KC, Gong EM, Orvieto MA, et al. Comparison of laparoscopic radical and partial nephrectomy: effects on long-term serum creatinine. *Urology* 2007;69:1035-40.
12. Thompson RH, Boorjian SA, Lohse CM, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol* 2008;179:468-71; discussion 72-3.
13. Huang WC, Elkin EB, Levey AS, et al. Partial nephrectomy versus radical nephrectomy in patients with small renal tumours–is there a difference in mortality and cardiovascular outcomes? *J Urol* 2009;181:55-61; discussion 61-2.
14. *Guideline for Management of the Clinical Stage 1 Renal Mass*. American Urological Association Education and Research, Inc. 2009.
15. Raj GV, Iasonos A, Herr H, et al. Formulas calculating creatinine clearance are inadequate for determining eligibility for Cisplatin-based chemotherapy in bladder cancer. *J Clin Oncol* 2006;24:3095-100.
16. Stevens LA, Coresh J, Greene T, et al. Assessing kidney function–measured and estimated glomerular filtration rate. *N Engl J Med* 2006;354:2473-83.
17. Clark AT, Breau RH, Morash C, et al. Preservation of renal function following partial or radical nephrectomy using 24-hour creatinine clearance. *Eur Urol* 2008;54:143-9.
18. Song C, Bang JK, Park HK, et al. Factors influencing renal function reduction after partial nephrectomy. *J Urol* 2009;181:48-53; discussion 53-4.
19. Fehrman-Ekholm I, Norden G, Lennerling A, et al. Incidence of end-stage renal disease among live kidney donors. *Transplantation* 2006;82:1646-8.
20. Najarian JS, Chavers BM, McHugh LE, et al. 20 years or more of follow-up of living kidney donors. *Lancet* 1992;340:807-10.
21. Lane BR, Babineau DC, Poggio ED, et al. Factors predicting renal functional outcome after partial nephrectomy. *J Urol* 2008;180:2363-8; discussion 2368-9. Epub 2008 Oct 18.
22. Kim HL, Shah SK, Tan W, et al. Estimation and prediction of renal function in patients with renal tumour. *J Urol* 2009;181:2451-60; discussion 60-1.
23. Pettus JA, Sharp DS, Yossepowitch O, et al. Tumour location does not affect long-term renal function after partial nephrectomy. *Urology* 2007;69:1059-63.
24. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(2 Suppl 1):S1-266.
25. Breau RH, Dahm P, Fergusson DA, et al. Understanding results. *J Urol* 2009;181:985-92. Epub 2009 Jan 16.

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